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Risk for Depression and Neural Responses to Fearful Facial Expressions of Emotion.

Key words: risk for depression, neuroticism, facial expressions, fMRI, amygdala, fusiform gyrus

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ABSTRACT

Background: Depression is associated with neural abnormalities in emotional processing.

Aims: This study explored whether these abnormalities underlie risk for depression.

Methods: We compared the neural responses of high-risk and low-risk never-depressed volunteers during the presentation of fearful and happy faces using fMRI.

Results: High-risk volunteers demonstrated linear increases in response in the right fusiform gyrus and left middle temporal gyrus to expressions of increasing fear while low-risk volunteers demonstrated the opposite effect. High-risk volunteers also displayed greater responses in the right amygdala, cerebellum, left middle frontal and bilateral parietal gyri to medium levels of fearful vs. happy expressions.

Conclusions: Risk for depression is associated with enhanced neural responses to fearful facial expressions similar to those observed in acute depression.

Declaration of Interest is listed at the end of the article.

INTRODUCTION

Facial expression processing bias is one of the most remarkable cognitive-social impairments in depression. Depressed patients have biases towards the perception of negative facial expressions such as fear and sadness, and / or away from happiness or other positive expressions (1-4). Functional imaging studies have outlined the neural basis of these behavioural biases. Specifically, depression is associated with elevated responses in the amygdala, insula and ventral striatum during the presentation of fearful or sad expressions (5-10). Aberrant neural responses have also been implicated in extrastriate areas such as the fusiform gyrus and cuneus (8, 10-12), possibly mediated via rich interconnections with amygdala circuitry (13, 14). These emotional processing biases in depression may be important in the underlying aetiology of this disorder, with patients assigning more salience and attention to negative vs. positive social cues, thereby fuelling negative thinking, poorer social function and increased access to negative memories. However it remains unknown whether such biases develop prior to the initial onset of depression. Neuroticism (N) is one of the best predictors of vulnerability to depression (15, 16) and we therefore sought to explore the neural substrates of facial expression processing biases in high risk (high N) vs. low risk (low N) never-depressed volunteers using functional Magnetic Resonance Imaging (fMRI). Previous work has suggested that linear modeling of the neural response to different intensities of positive and negative emotions is a sensitive way of identifying biases in depression (7, 8, 17). Thus we hypothesized that similar biases would be seen as a function of vulnerability *per se*. Specifically we hypothesized that high N would be associated with increased neural responses to increasing intensity levels of fear and / or reduced responses to increasing intensity of happiness within the amygdala and fusiform gyrus in line with previous studies on depression (5, 7, 8, 17, 18).

METHODS

Subjects

Twenty-five right-handed healthy volunteers (17 female, aged 18-22) gave written informed consent to the study, which was approved by the Oxford Research Ethics Committee. The Structured Clinical Interview for DSM-IV (19) was used to verify that all subjects were free of current or past axis-1 disorders, and all of them were free of medication apart from contraceptive pills. Participants received payment for their participation. These participants were a subset of those previously taking part in the behavioural assessment of emotional processing (20), but the testing sessions were on average 11 months apart.

N scores were derived from the 12-item neuroticism scale of the shortened Eysenck Personality Questionnaire (EPQ: 21). Twelve (9 women) were in the high neuroticism group (N range 8-12), and 13 (8 women) in the low neuroticism group (N range 0-3). This range of N scores was consistent with our previous behavioural study (20). The two groups were matched for age (mean 20.00, SD 0.60 vs. mean 20.15, SD 0.99), gender, verbal IQ (mean 119.10, SD 3.03 vs. mean 118.66, SD 4.26) and spatial IQ (in ms, mean 2584, SD 941 vs. mean 1974, SD 610) assessed by NART (22) and WAIS-R (23) respectively. Two participants had a first degree relative with depression (one from each group).

Mood Variables

The Beck Depression Inventory (BDI; 24) and State-Trait Anxiety Inventory (STAI; 25) were used to assess self-rated mood.

Stimuli and Task

Each volunteer participated in a single 16 minute experiment employing rapid event-related fMRI. Eight faces (4 male, 4 female) displaying prototypical expressions of fear and happiness were taken from a standardized series of facial expressions (26). In addition to the prototypic or high intensity (100%) facial expression, medium (60%) and low (30%) intensity expressions generated using morphing software (27) were used. Each face was also presented in a neutral facial expression. Thus, there were eight facial stimuli representing each of the following categories: high fearful (fear-H), medium fearful (fear-M), low fearful (fear-L), high happy (happy-H), medium happy (happy-M), low happy (happy-L), and neutral. Each of these faces was presented three times and 24 presentations of a fixation cross were included as baseline, giving a total of 192 trials. Stimuli were presented in a random order for 500ms each, and the intertrial interval varied according about a Poisson distribution with a mean of intertrial interval of 5000ms. Subjects were asked to indicate the gender of each face by pressing one of two keys on an MRI compatible keypad. No motor response was required for baseline trials of fixation cross. Stimuli were presented on a personal computer using E-Prime (version 1.0; Psychology Software Tools Inc., Pittsburgh, PA) and projected onto an opaque screen at the foot of the scanner bore, which subjects viewed using angled mirrors. Behavioural responses were recorded using a MRI-compatible keypad. Accuracy and reaction times were recorded by E-Prime.

fMRI Data Acquisition

Imaging data was collected by a 1.5T Siemens Sonata scanner located at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). Functional imaging consisted of 30 contiguous T_2^* -weighted echo-planar image (EPI) slices [repetition time (TR) = 3000ms, echo time (TE) = 50ms, matrix = 64 x 64, field of view (FOV) 192 x 192, slice thickness 4mm]. A Turbo FLASH sequence (TR = 12ms, TE = 5.65, voxel size = 1mm³) was also

acquired to facilitate later coregistration of the fMRI data into standard space. The first two EPI volumes in each run were discarded to ensure T_1 equilibration.

Data Analyses

Functional MRI data analysis was carried out using FSL version 3.2 β (28). Preprocessing included slice acquisition time correction, within-subject image realignment (29), non-brain removal (30), spatial normalisation (to Montreal Neurological Institute [MNI] 152 stereotactic template), spatial smoothing, and high-pass temporal filtering (to a maximum of 0.025Hz).

In the first level analysis, individual activation maps were computed using the general linear model with local autocorrelation correction (31). Eight explanatory variables were modelled, including each intensity (low, medium, high) of fear and happy as well as neutral and fixation. The main contrasts of interest were fear vs. happy expressions (and vice versa) for each intensity level, i.e. fear-H vs. happy-H; fear-M vs. happy-M, fear-L vs. happy-L. In addition, each individual activation map was analysed by fitting linear trends at each voxel at the three intensity levels of fear and happy, separately, with orthogonal polynomial trend analysis. Positive linear trends modelled responses for increasing emotional intensity while negative linear trends modelled responses for decreasing emotional intensity. All variables were modelled by convolving the onset of each stimulus with a haemodynamic response function, using a variant of a gamma function (i.e. a normalisation of the probability density function of the gamma function) with a standard deviation of 3s and a mean lag of 6s.

In the second level analysis, individual data were combined at the group level (high N vs. low N) using a mixed effects analysis (32). This mixed effects approach accounts for intra-subject

variability and allows population inferences to be drawn. We aimed to establish, first, the effect of neuroticism on the responses to fear vs. happy facial expressions at each intensity level; and second, the effect of neuroticism on the linear trend across increasing or decreasing intensity of fear and happy expressions. Significant activations were identified using a cluster based threshold of statistical images [height threshold of $Z = 2.0$ and a (corrected) spatial extent threshold of $p < 0.05$ (33)]. Significant interactions were further explored by extracting percent BOLD signal change within the areas of significant difference, which were then analysed using repeated measures ANOVA (between Ss variable = group; within Ss variable = intensity or valence) followed by appropriate *post hoc* t-tests (SPSS v.14.0). Corresponding Brodmann Areas (BA) were identified by transforming MNI coordinates into Talairach space (34).

Due to the strong *a priori* evidence implicating the amygdala in the processing of facial expressions (5-9), we also performed a region-of-interest (ROI) analysis. Amygdala masks (left and right) were segmented for each individual using a robust fully automated Integrated Registration and Segmentation Tool ("FIRST"; 35). Percent BOLD signal change for each emotional stimulus (fear and happy) was extracted from each individual amygdala. These data were entered into 2x2x3 repeated measures ANOVA (between Ss variable = group; within Ss variables = valence or intensity). Significant three-way interaction was clarified by two-way ANOVA and subsequent t-tests.

For the behavioural data, independent samples t-tests were used to examine group difference for subjective mood ratings, overall accuracy and reaction time of the gender discrimination responses. Due to technical difficulties, reaction time and accuracy data (measured during fMRI) from four low N subjects were not recorded. These subjects were included in the

analysis of fMRI data because the behavioural response of gender discrimination is incidental to the main outcome measure of neural response to emotional valence.

RESULTS

Mood Ratings and Behavioural Data

As expected high N subjects had significantly higher scores on trait anxiety (mean 39.00, SD 8.15 vs. mean 27.47, SD 4.91, $p=0.00$) and a non-significant trend of higher scores on state anxiety (mean 32.08, SD 7.09 vs. mean 26.46, SD 7.02, $p=0.06$). There was no significant group difference in BDI scores (mean 2.50, SD 1.93 vs. mean 1.23, SD 1.92, $p=0.11$). Behaviourally, both groups achieved higher than 90% correct for gender discrimination of all facial expressions, with no between-group difference (mean 94.29, SD 5.62 vs. mean 92.80, SD 9.51, $p=0.66$) and did not differ in overall reaction time (mean 674.38, SD 87.29 vs. mean 725.97, SD 161.84, $p=0.36$).

Functional Imaging Results

Neural Responses for Fearful vs. Happy Expressions: Between-Group Differences

Our primary hypothesis was that fearful and happy faces would be differentially processed by the subject groups. Indeed, high N vs. low N subjects exhibited greater activity for fear vs. happy expressions with medium intensity (i.e. fear-M vs. happy-M) in the following areas: cerebellum (MNI: 0, -64, -26, $z=3.91$), left middle frontal gyrus (BA10, MNI:-30, 58, 2, $z=3.46$), left superior parietal (BA7, MNI:-18, -66, 60, $z=3.25$) and right superior parietal cortex (BA7, MNI: 4, -48, 68, $z=3.25$). Analysis of percent BOLD signal change for fear-M and happy-M stimuli revealed increased responses in high N subjects during presentation of fearful facial expressions, which in some areas was accompanied by relatively reduced responses during the presentation of happy facial expressions (see Figure 1 for simple main effect analyses). These effects remained significant after including BDI or STAI scores as covariates (all $p<0.01$).

[Figure 1 about here]

Linear Trend for Increasing Intensity of Fear or Happiness: Between-Group Differences

For fearful expressions, high N subjects demonstrated a significant positive linear trend in right fusiform gyrus (BA 19, MNI: 26, -66, -14, $Z=3.48$, see Figure 2) and left middle temporal gyrus (BA21, MNI: -56, -32, 0, $z=3.51$, see Figure 3) relative to low N subjects. Further analyses of percent BOLD signal change confirmed a significant group-by-intensity interaction in both fusiform gyrus ($F(2, 46) = 14.155$, $p<0.001$) and middle temporal gyrus ($F(2, 46) = 18.736$, $p<0.001$), which remained significant after including mood scores (BDI, STAI) as covariates (all $p's \leq 0.001$). In right fusiform gyrus, high N subjects showed greater activation for increasing fearful intensity whereas low N subjects showed the opposite effect (Figure 2). *Post hoc* t-tests revealed greater activation in high N subjects for the high intensity of fear ($p=0.006$) and a marginal reduction in activation for low intensity of fear ($p=0.060$). A similar pattern was found in middle temporal gyrus (Figure 3), in which high N had greater activation for high intensity ($p<0.001$) and reduced activation for low intensity ($p=0.001$) of fearful expressions. By contrast, there was no between-group difference in terms of linear trends for happy expressions.

[Figures 2 & 3 about here]

ROI Analysis of Amygdala Responses

Amygdala volumes were not significantly affected by group (main effect of group: $F(1,23)=0.563$, $p=0.461$; group x hemisphere: $F(1,23)=0.261$, $p=0.614$), allowing functional responses to be examined in the absence of potentially confounding structural differences. In the right amygdala there was a non-significant trend for an emotion x intensity x group

interaction ($p=0.092$). Due to the strong *a priori* hypothesis regarding the effects on ambiguous facial expressions, two-way ANOVAs were run for each intensity level. These revealed a significant group x valence interaction for medium intensity (i.e. fear M vs. happy M; $p=0.024$). This interaction was driven by high N having greater amygdala activation for medium fearful expressions relative to the low N group ($p=0.029$; see Figure 4). By contrast, there was no significant effect in the left amygdala.

[Figure 4 about here]

DISCUSSION

To our knowledge this is the first study to demonstrate the neural basis for negative biases in emotional facial processing in subjects at high risk for depression by virtue of high neuroticism. Our high N never-depressed volunteers exhibited a linear increase in neural signals in right fusiform gyrus and left middle temporal gyrus for increasing intensity of fearful expressions, whereas the low N volunteers showed the opposite effect. Furthermore, high N volunteers showed a larger response in right amygdala, cerebellum, left middle frontal gyrus, and bilateral superior parietal cortex during the presentation of ambiguous medium levels of fearful vs. happy expressions. These areas have been implicated in facial expression processing and depression in previous studies. We believe we have demonstrated neural processes which may be involved in vulnerability to depression.

A key role for the amygdala and the fusiform gyrus in facial expression recognition and depression has been proposed previously from studies of currently depressed individuals (5,7,8,17,18) and a similar pattern of effect was seen here as a function of neuroticism. Thus, the increased responses shown by high N volunteers for increasing intensity of fear in the right fusiform gyrus and heightened amygdala responses to ambiguous fearful facial expressions are similar to those observed in depressed patients (5, 8). Vulnerability to depression has also been associated with aberrant amygdala responses to negative facial expressions in subjects with familial risk for depression (e.g. 36, 37). These results are also consistent with recent evidence which suggests that amygdala responses to emotional information correlates with neuroticism scores in unselected populations (38, 39). Together these findings suggest that increased amygdala responses to negative affective stimuli may be involved in risk for depressive disorders.

It is notable that while high N volunteers showed the expected increase in fusiform response as a function of increasing fear value, the low N volunteers showed the opposite pattern. This implies decreased visual processing with increasing fear in volunteers at low risk of developing depression. Perception of fearful faces is believed to convey social signals of threat or danger (13, 40). Such a pattern of effect could be explained by differential evaluation of threat value in high vs. low N volunteers, according to the curvilinear response function of the cognitive motivational account (41). This theory suggests that low threat stimuli may be avoided in order to reduce distraction while high threat stimuli are monitored for potential importance. The observed pattern of results would be expected if low N volunteers estimated the face stimuli as having a lower threat value, leading to the high intensity fearful faces being perceived as low threat and thus ‘avoided’. In other words, the current observation of reducing neural responses towards fearful expressions with higher intensity suggest that low risk for depression may be manifest as a reduced estimation of threat value in the environment.

In addition to the effects on the fusiform gyrus and amygdala, our results implicate a network of brain areas that are involved in facial processing and vulnerability to depression. First, the middle temporal gyrus revealed differential responses for fearful expressions in high and low N volunteers similar to that observed in the fusiform gyrus. The temporal gyrus is within the core system of face perception (13, 42) and the increased responses seen here in high N volunteers appear to be consistent with greater processing of threat relevant facial stimuli in this group.

The medium intensity of fear versus happy expressions revealed group differences in the left middle frontal gyrus, and bilateral parietal cortex. Indeed, such a frontoparietal network plays a central role in the concept of self, perception of social relationships and attention (e.g. 43, 44). Thus, the specific activations for fearful expressions in these regions by high N individuals could be explained by their greater tendency to view negative expressions as self-relevant or self-threatening and thereby requiring activation of attentional systems. In line with this, the reduced activation for happy expressions may reflect their inclination to disregard positive social information as self-referent and deserving of further attention. In other words, these individuals are more likely to interpret negative social signals to be personally relevant or threatening, but at the same time unable to translate positive social signals for positive self regard. This interpretation is consistent with the self-referent and facial expression processing biases observed in a similar high N sample (20).

The same analysis also revealed increased cerebellum responses in the high N volunteers towards fearful vs happy facial expressions. The cerebellum is well known to play a key role in fear conditioning, anticipation of pain and co-ordination of motor action (45-48). Its role in processing fearful facial expressions is therefore not unexpected and the greater response in the high risk volunteers may represent either greater conditioned responses or increased readiness for action (49), potentially mediated via increased drive from limbic areas.

The current study demonstrated differential responses to emotional cues in the high N group in the absence of current or past Axis 1 psychiatric disorders from DSM-IV, thereby indicating that these biases exist prior to mood or anxiety disorder. Analyses including mood scores as covariates confirmed that the current effects were a function of neuroticism *per se* independent of mood state. The absence of family history of depression in the high N group

further suggested that the aberrant signals found in high risk group were a function of high neuroticism *per se* independent of familial risk for depression. As noted in the introduction, neuroticism has been identified as a robust predictor for depression. For example, Kendler and colleagues (15) found that a 1-SD difference in neuroticism translates into a 100% difference in the rate of first onsets of depression over 12 months. Similarly, in a recent report based on a large Swedish twin sample (>20000 individuals; 16), neuroticism strongly predicted the risks for lifetime and first onset depression assessed in 25-years follow up. Thus, the differences in neural response to positive and negative affective stimuli seen here may be involved in predisposition to depression, consistent with cognitive theories of depression.

The differential responses for positive vs. negative expressions shown here were seen largely with the medium intensity level of facial expression. This probably represents maximal ambiguity as behavioural data suggests that low intensity levels are usually perceived as neutral and high intensity levels usually elicit ceiling levels of performance, with the longest reaction time to identify facial expressions being seen around mid-intensity level (50, 51). Such ambiguous social signals may be particularly relevant for problematic social interaction and, experimentally, for differentiating group differences. The current findings were also obtained from direct contrast between positive and negative emotional stimuli, which avoided potential confounds linked to the interpretation of neutral stimuli. The current study specifically investigated the emotional processing of fearful and happy expressions, which have been previously shown to be affected by depression and its treatment (e.g. 5, 52). However, risk for depression may also be related to negative biases in the perception of other expressions such as sadness as previously seen in depression (3, 4, 7).

Our behavioural study on a similar high N vs. low N sample found a decrease in the recognition of happy facial expressions in the absence of differences in the threshold for perception of fear (20). In other words, the neural bias towards negative stimuli does not appear to be simply translated into a behavioural bias to detect negative expressions more easily. The observed biases do not necessarily give rise to current depression or anxiety but may remain latent until triggered by stress or decreased mood.

Finally, the current study has a number of limitations. The generalization of the current finding could be potentially limited by the relative small sample. Although high neuroticism is a robust risk factor for depression, the relatively low prevalence rates of depression imply that only a small proportion of the high N population will go on to develop depression, thereby potentially diluting any effects that we may have seen. Longitudinal studies are required to assess the predictive power of negative biases for subsequent depression in a sample adequately powered for the detection of infrequent events. In addition, in the current study the experimenters were not blind to group membership. Although this is unlikely to have an influence on the results because responses were collected automatically and task instructions were standardized across participants, future studies may want to assess negative bias using a blinded design to confirm these findings.

In conclusion, our results illuminate the role for a distributed neural network, including the fusiform gyrus and amygdala, in facial expression processing biases in volunteers at high risk for developing major depression. These areas overlap with those thought to be important in depression and those targeted by antidepressant drug administration (5, 7, 12). Longitudinal

studies are underway to estimate whether, and to what extent, this aberrant neural behaviour predicts onset of depression.

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All authors listed on the article have made substantial contribution to the present work and therefore met full criteria for authorship. Stella Chan contributed to the design of the experiment, collection, analysis and interpretation of data, and drafting of the paper. Raymond Norbury provided substantial technical support for the design of the experiment, collection, analysis and interpretation of data, and revision of the paper for important intellectual content. Guy Goodwin gave substantial contribution to the conception and design of the experiment and revised the paper for important intellectual content. Catherine Harmer gave substantial contribution to the conception and design of the experiment, interpretation of data, and critical revision of the paper. All authors approve of the present version of the paper to be published.

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TITLES AND LEGENDS TO FIGURES

Figure 1: The image and BOLD percent signal change of the brain regions where high N volunteers (black) showed greater activation for fearful vs. happy faces at medium intensity than low N volunteers (white). Colour bar represents Z score between 2.0 and 3.9. Asterisks (*) represent significant group comparisons $p < 0.05$.

Figure 2: The image and BOLD percent signal change of right fusiform gyrus (MNI: 26, -66, -14), in which high N volunteers (black) showed increased signals for increasing intensity of fearful expressions whereas low N (white) showed the reversed pattern. Colour bar represents Z score between 2.0 and 3.5. Asterisks represent significant group comparison $p < 0.05$.

Figure 3: The image and BOLD percent signal change of left middle temporal gyrus (MNI: -56, -32, 0), in which high N volunteers (black) showed increased signals for increasing intensity of fearful expressions whereas low N (white) showed the reversed pattern. Colour bar represents Z score between 2.0 and 3.5. Asterisks represent significant group comparison $p < 0.05$.

Figure 4: Percent BOLD signal change in right amygdala for fearful and happy expressions at medium intensity by high N (black) and low N (white) volunteers. Asterisks represent group comparison $p < 0.05$.